# **Biometry Branch:** Summary Statement

## by David G. Hoel

The primary mission of the Biometry Branch is to conduct applied research in the areas of biomathematics, epidemiology, and risk assessment. The Branch also provides statistical, mathematical, data processing and computer engineering support to the Institute.

Biomathematics, which is essentially a collaborative effort involving a variety of scientific disciplines, focuses on mathematical modelling of biological processes. At the present time the major areas of interest are mathematical population genetics and pharmacokinetic modelling. The Branch's epidemiological research is concerned with the evaluation of the impact on human health of exposure to environmental levels of various potentially hazardous compounds. Hazard assessments are made directly through actual field studies as well as indirectly by the analysis of pre-established data bases. In addition, methodological research directed toward improved planning and evaluation of epidemiological studies is conducted. Risk assessment activities have emphasized the improvement of the use of data generated from animal screening studies to estimate long-term human risk from exposure to ambient levels of chemical carcinogens. Research efforts range from the development of sophisticated mathematical models for extrapolation to the investigation on an applied, semiquantitative basis of species differences in response to carcinogenic agents.

Statistical support given to Institute intramural scientists spans the spectrum of consulting activities from design of pilot studies to analysis of data generated at the conclusion of large-scale, long-term experiments. Computer support covers such diverse activities as the development of information retrieval and inventory maintenance systems, the simulation of complex biological models designed to clarify mechanistic processes, and the provision of computer engineering support for real time and minicomputer data acquisition and controls systems.

#### **Biomathematics**

Research is underway in two areas of mathematical biology. Both programs involve collaboration with experimental scientists in other branches.

Joint research with the Laboratory of Environmental Mutagenesis is being conducted on problems in population genetics theory. The long-range objective of this work is to develop a better understanding of environmental effects on gene frequency distributions. A model for spatial dispersion of neutral alleles was used in conjunction with drosophila data to indicate the improbability of the same neutral allele appearing at widely separated localities. Some mathematical results needed to study the effect on natural selection of autocorrelated changes in the environment were obtained. A probabilistic relation between the age of a neutral allele and its frequency was derived.

In collaboration with the Laboratory of Pharmacology, research efforts in pharmacokinetics were concentrated in two areas: whole body distribution and modeling studies and uptake storage, metabolism, and release of pollutants and model compounds by isolated perfused organs, with present emphasis on liver and lung. The kinetics of chemical disposition in whole body and isolated organs are being determined in order to construct mathematical models of these processes which can be used: to better define and understand ratelimiting steps in the process, to extrapolate distribution profiles of chemicals from one tissue to another, one species to another, and to man; and to predict tissue storage of pollutants from knowledge of routes, dose, and numbers of exposures. The disposition of five polychlorinated biphenyls (PCB) isomers was studied in the rat and mouse. Pharmacokinetic models have been developed for the rat and these can be scaled to the mouse. Disposition data are being obtained for the same compound in the dog and monkey so that species-to-species extrapolation of disposition profiles can be made.

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Several of these compounds have extremely long half-lives of storage in skin and fat. The pharmacokinetic models will be used to predict accumulation from long term low-level exposure. The disposition of a polybrominated biphenyl, 2,4,5,2',4',5'-hexabromobiphenyl, has also been investigated. The rat is essentially incapable of metabolizing this compound and hence its half-life is greater than the life span of the animal. Pharmacokinetic models have also been developed for this compound and prediction of accumulation from chronic dosing is possible. The correlation of pharmacokinetic parameters with toxicological parameters is under investigation.

#### **Risk Assessment**

Use of data from animal experiments to estimate the human risk from long-term exposure to very low doses of environmental carcinogens poses a number of biological, pharmacological, and statistical problems. One of the statistical problems is to extrapolate the animal dose-response relations from the high dose range where animal test data are available to low doses which humans might encounter. Different techniques which would seem to fit the test data equally well can lead to low dose risk estimates that differ by several orders of magnitude. The purpose of this project is to evaluate existing methods and to develop new statistical methods for risk estimation and animal test design, reflecting current understanding of carcinogenic mechanisms.

Methods for low-dose extrapolation based on the Armitage-Doll multistage carcinogenesis model were incorporated into computer programs and used to estimate the cancer risk associated with a number of different chemicals, including some trace impurities in drinking water. Computer programs were developed to simulate patterns of doseresponse data such as are obtained in animal carcinogenesis experiments. These programs are being used to investigate the statistical uncertainty in low-dose extrapolations from animal experiments and to make a preliminary exploration of some considerations in the statistical design of such experiments. Statistical methodology was developed for some hypothesis tests associated with low-dose extrapolations. The computer programs used in this work have been made available to other scientists at NIH.

Mathematical models to predict the effect of dose on cancer latency period were investigated. This work was motivated by data which had been cited in the literature as implying a physical increase in tumor growth time with decreasing dose. It was shown that the observed increase in average latency period could also be explained as a simple mathematical consequence of a decrease in incidence with decreasing dose; no physical increase in tumor development time need be postulated to explain the data. The average latency period and the minimum latency period in a small group of animals were both shown to be poor indicators of the risk of developing a tumor within a normal animal lifespan.

## **Epidemiology**

While the focus of the epidemiology program has remained unaltered, i.e., the identification of potential health hazards in the general environment, the scope of the program has been broadened considerably by the initiation of field studies for direct hazard assessment. One of the first issues that is being addressed by this mechanism is the evaluation of the possible excess risk incurred by breastfed infants as a result of their exposure to elevated levels of PCBs (polychlorinated biphenyls) in mother's milk. A prospective study has been launched to identify and assess the health status of a cohort of children at birth and then to periodically reexamine them over the first six months of life. Concurrently, breast milk and formula samples, as well as cord blood and placenta, will be tested for evidence of contamination. Although the study is initially restricted to the state of North Carolina, it is hoped that a flexible field methodology will be developed, allowing the problem to be evaluated in other locales while maintaining tight data comparability. Another environmental hypothesis that is being explored in an actual field setting is concerned with the potential effects of lead exposure on the cardiovascular system in children who have measurable body burdens of lead but are not clinically intoxicated.

In addition, statistical methodology problems relevant to epidemiological research continue to be investigated. These statistical investigations are directed at such diverse issues as the usefulness of ecological associations as a means of evaluating environmental risk, the estimation of prevalence rates through screening tests, and the assessment of synergism (or antagonism) by using epidemiologically based data.

## **Statistical Consulting**

While much of the Biometry Branch's focus is on its own research efforts, it also provides a statistical consulting service for the intramural research program. Statistical consulting is quite comprehensive in its scope, encompassing both experimental design and data analysis.

The design of experiments covers all types of investigations ranging from small-scale pilot studies to experiments concerned with the effects of lifetime exposures to potentially hazardous chemicals. Besides the usual emphasis on the maximization of design efficiency, special attention is given to the particular, practical constraints which confront the individual investigator. As a result, the assessment of study feasibility is one of the most useful consulting services provided in this area.

Data analysis involves the use of all the traditional parametric and nonparametric statistical procedures. For large data sets, or studies requiring the use of complex statistical methods, data analysis activities are closely coordinated with the Branch's computing work group. In addition to these services there is also a very active applied research effort directed toward the development of new methodology to meet some of the highly specialized analytical needs of the intramural program.

In order partially to relieve the increased consulting workload created by the expansion of the intramural research program, additional emphasis has been placed on the continuing development of self-help systems for routine data analysis. These systems have been made readily accessible to all Institute scientists and technicians. Moreover, a basic course on statistical design and analysis is now being offered to members of the intramural program, emphasizing the role which statistics should play in their various research efforts.

## Computing

Data processing efforts within the Biometry Branch fall into two distinct areas: those directed principally to tasks within the branch, and those dealing primarily with providing data processing and computer engineering services to the Institute at large.

Numerous projects in the latter category have received support. Those of an administrative nature include a computerized warehouse inventory management system, a periodically updated listing of all radioisotopes held at NIEHS, a budget-reporting system listing financial transactions and billings with summaries for each branch, and an animal ordering and inventory system.

In support of intramural research, major efforts have been conducted in the fields of protein receptor analysis for the Developmental Toxicology section, assessment of synergism for the Inhalation Toxicology section, and gene frequency deviation detection with Monte Carlo simulation of related

phenomena for the Population Genetics section. The Pharmacokinetics section continues to expand its use of computing facilities. In addition to this section's on-going analyses of pharmacokinetic data, numerical methods requiring extensive computational power are under development. These techniques will provide the mathematical modelling and computer simulation facilities needed for interspecies extrapolation of low-level, long term pharmacokinetic profiles.

A capability for providing computer engineering support to the laboratories of the Institute is presently being developed within the Biometry Branch Solutions will be sought to engineering problems related to all aspects of computer hardware and instrumentation programming. The tasks of this effort to date have involved the specification of minicomputers, peripherals, and operating system software; the design of interfaces between these minicomputers and laboratory instruments; and the development of software for control of experiments, data acquisition, and data transmission. The following major tasks are currently underway. (1) For the Laboratory of Environmental Mutagenesis, computer programs are being developed for the PDP-12/Zeiss system for absorption measurements of stained sperm cells and partially automated measurement of mutation frequency in sperm and red blood cells. As this research project progresses, hardware and software will be recommended for the fully-automated measurement of mutation frequency. (2) A network of minicomputers has been recommended for the Behavioral Toxicology Program. Interfaces between these computers and the behavorial apparati are being designed and built. (3) For the Laboratory of Environmental Mutagenesis. a small minicomputer system is being developed for the automatic acquisition and storage of data from a Gilford spectrophotometer. Also an X-Y digitizer will be interfaced to this computer for measurement of DNA molecules.

Within the Biometry Branch, substantial efforts have been directed toward improving the general data processing capability, particularly as it affects the computing needs of those providing statistical data analysis in support of the intramural research program. The Institute's PDP 11/40 computer has been significantly expanded with the addition of various peripherals and the implementation of a multi-programming operating system. This computer is heavily used both to provide high-speed telecommunications to the NIH IBM/370 system and to accomplish a great variety of local computing activities.

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